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Fit and misfit between ligands and metal ions

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Contents

Abstract

Multidentate and in particular macrocyclic and rigid ligands may enforce a particular structure on a metal complex. Molecular properties, such as stabilities, reduction potentials, reactivities and spectroscopic properties depend on the molecular structures, and molecular properties may, therefore, be tuned by the ligand architectures. Approaches to predict structures and properties will be briefly reviewed and important concepts, including ligand preorganization, complementarity, flexibility, elasticity and energization (entatic states) will be discussed in detail.

Keywords: Preorganization; Complementary; Entatic state; Flexibility; Elasticity

1. Introduction

The recognition of a substrate by an enzyme, that of a guest by a supramolecular host and that of a metal ion by a ligand have in common that properties of all of the corresponding complexation products depend on whether, in which way and how much the two partners fit together. One of the most fundamental and first thoughts in this area is the lock-and-key concept [1], which has been and still is stimulating research in biochemistry, supramolecular and classical transition metal coordination chemistry. An important step forward was the perception that the structure of enzyme active sites can be structurally modified by substrate binding, and this was the basis for the induced-fit model for enzyme-substrate interactions [2]. The strain induced in the substrate by the host (and vice versa) may lead to some energization, and this was recognized as an important factor in enzyme catalysis and defined as the entatic state principle [3]. Thus, the rigidity (or flexibility and elasticity, see below for the definition of and differentiation between flexibility and elasticity) of

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the host and the host-guest complex are important factors for both molecular recognition and catalytic activity.

The definition and fundamental applications of fit and misfit between host and guest emerged from studies at the interface between biological, supramolecular and classical coordination chemistry: recognition and selectivity with respect to a specific host-guest couple imply a high degree of ligand (host) preorganization and host-guest complementarity [4,5]. An important observation is that the fit between a host and a guest (complementarity) is not only a geometric, i.e. a classical lock-and-key problem, the interactional complementarity between host and substrate (electronic factors, bonding) also is of importance, and this amounts to the generalized double complementarity principle [6,7].

While concepts related to fit and misfit emerged mainly from biochemistry, bioinorganic and supramolecular chemistry they have attracted the interest of classical coordination chemists for some time. It appears that the question of how ligands and metal ions fit together is of importance in the fields of metal ion recognition (metal ion selectivity, stabilization of one metal complex over others) [8–10], catalysis (entatic states, selective activation of a specific reaction channel) [11], as well as spectroscopy and redox processes of transition metal compounds [12–14].

The aim of this publication is to thoroughly analyze the concepts of preorganization, complementarity and entatic states, primarily in the area of classical coordination chemistry. While it is obvious that the type of donor atoms and the solvation of metal ions, ligands and complexes are of importance for the stabilization of complexes with specific metal ions in specific oxidation states and electronic configurations, we fully concentrate here only on geometric factors as the basis for preorganization and complementarity (remember the note above on the generalized double complementarity principle). The main focus, therefore, is on how ligands can enforce a given structure, how conformational flexibility can be suppressed and how the elasticity of an enforced conformation can be reduced. Enhanced complex stability and metal ion selectivity are just one application of these concept and are not the only or main focus of this account. Computational methods have proven to be of importance in a careful analysis of structural, dynamic and, to some extent, thermodynamic properties of metal complexes. These include the statistical analysis of experimental structural data, conformational analyses based on molecular dynamics and Monte–Carlo searches, structure optimization and the analysis of the shape and elasticity of ligands and complexes, and these involve molecular mechanical and quantum mechanical approaches. Technical details, strengths and weaknesses of these methods, as well as the interpretation of extensive data sets are not discussed here.

2. Structures and properties

The structure of a molecule is defined by the arrangement of atoms with a given connectivity and configuration; in the ground state of the molecule the structure is a local minimum on an energy surface. The energy difference between various local minima (conformations) defines their relative abundance in the thermodynamic equilibrium, and the dynamics (conformational flexibility) depends on the corresponding energy barriers. The free energy of each structure, i.e. the stability of a compound in a specific geometry, is a function of all possible interactions of all atoms with each other. In a stable compound all groups fit well together. Misfit between various fragments, e.g. the metal center and the ligands, leads to thermodynamic and kinetic instability. Structural distortion results also in spectroscopically detectable electron redistribution. That is, electronic properties are related to structural parameters, i.e. spectroscopic parameters are a function of structure, as are stabilities and reactivities.

The geometry of transition metal compounds is a compromise between the metal ion and ligand preferences. As bonds in organic molecules and angles around carbon and the common main group hetero atoms are usually strong in comparison with metal-donor interactions ligands can enforce the structure in classical transition metal coordination compounds. Rotations around single bonds are the only low energy modes in the ligand backbone, and these lead to conformational flexibility and a reduction of the power of the ligand to enforce specific properties on the complex. Multiple bonds and substitution of the ligand backbone can be used to increase the rigidity of the ligand [11,12,14].

The preparation of novel coordination compounds with specific properties requires a thorough understanding of the electronics of metal centers [15–19] and the know-how and patience to design and prepare exciting ligands which allow to efficiently tune them. Methods for modeling molecular structures and properties have been reviewed extensively (for a recent overview see reference [20] and papers cited therein).

3. Preorganization and complementarity

With a given donor set and metal ion the thermodynamic stability of a metal complex is primarily related to ligand preorganization and metal–ligand complementarity [4,5,8,21]. It follows that ligand preorganization and complementarity are related to a specific metal complex. A metal-free ligand with the same conforma-

tion as in the complex with a specific metal ion is highly preorganized for this metal ion[1]. A structurally complementary ligand has an ideal size and shape for a specific metal ion. That is, the spatial distribution of the donor atoms in the metal-free ligand in the conformation which coordinates is that preferred by the specific metal ion, and the lone pair directions are similar to the donor-metal directions in the complex[2]. Note that ligand preorganization is defined with respect to a specific coordination geometry, and this may obviously depend on the electronic preference of the metal ion (e.g. four-coordinate copper(I), no preference vs. four-coordinate copper(II), planar) and in some cases also on its size (e.g. folding of tetraazamacrocyclic ligands with large metal ions, i.e. *cis*-octahedral vs. *trans*-octahedral configuration). The relative sizes (cavity vs. metal ion) are of importance for the ligand complementarity; therefore, this is also defined with respect to a specific metal ion. For all issues discussed here the combination of preorganization and complementarity rather than one of these properties alone are of importance.

4. Entasis

Misfit between two fragments to be bound to each other leads to destabilization of the complex. In a catalyst-substrate adduct this energization is the basis for a selective activation of the substrate, i.e. the substrate may be 'squeezed' by the catalyst and the energization results in the reduction of the energy barrier for a specific reaction channel for substrate derivatization. Another important feature is that ligands may distort the coordination geometry of a catalyst in a particular way and, therefore, deform the electron distribution of the metal center such that specific electronic and oxidation states of the catalyst are stabilized. Bonding of a substrate to such a complex fragment may lead to a structural distortion and energization of the coordinated substrate and, therefore, to a deformation of the electronic configuration and a corresponding activation. The kinetic features emerging from these mechanisms are the basis of the entatic state principle [3,11,22,23].

[1] In addition, a highly preorganized ligand has only weakly solvated donor atoms [4,5]. Often this is discussed as a separate issue and in the present publication we concentrate exclusively on geometric factors.

[2] Note that this requires a thorough knowledge of the geometric preferences of the metal ion and of the ideal metal-donor distances, i.e. complementarity is not a quantitatively unambiguous property [18].

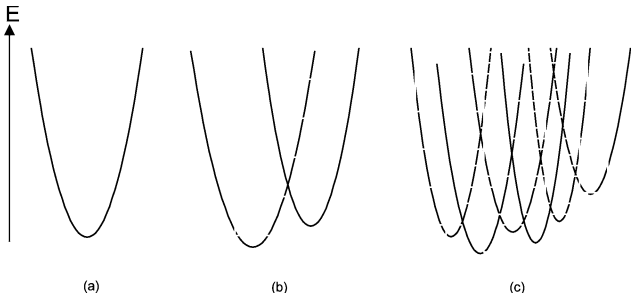


Fig. 1. Hole size curves (shape, size, elasticity and flexibility of ligand cavities). Plotted is the potential energy (usually the steric energy, molecular mechanics) of a ligand as a function of the distance of the donor atoms to a fictive metal center; (a) a single isomer (configuration or conformation), i.e. an inflexible ligand; (b) two isomers; (c) multiple isomers (flexible ligand).

5. Rigidity, flexibility and elasticity

A straight forward but not comprehensive conclusion of the last paragraphs is that the size and shape of the ligand cavity influence the host-guest (metal–ligand) stability and activity; a good fit leads to a stable complex, misfit to destabilization and/or entasis. It is appropriate here to discuss cavity (hole) size curves, which are often used to visualize the shape, size, flexibility and elasticity of ligand cavities (Fig. 1). Hole size curves are plots of the potential energy of a ligand or a complex as a function of the metal-donor distances. There are many possible ways to compute these, most frequently molecular mechanics is used. There have been vigorous arguments on which molecular mechanics approach is best suited to compute meaningful cavity size curves [8,9,14,18,24–26]. We use an approach, which allows for metal ion independence, to constrain the sum of bond distances mathematically and, therefore, it is also suitable for asymmetric ligands and the corresponding complexes [18,26].

A complex whose structure corresponds to the minimum of a cavity size curve (Fig. 1a) has optimum stability (ideal fit); misfit leads to a loss of stability (increasing strain)[3]. The steepness of the potential energy curve is related to the ligand elasticity (the ease of deformation of the ligand backbone). Such a curve is for a constant conformation, and, in particular for rigid ligands, deformations are, apart from relatively small distortions to dihedral angles, also due to bond distance and valence angle distortions.

Ligands generally have more than one accessible conformation. In the hypothetical case with two stable conformers with appreciably different hole size and

[3] Note that this only includes the geometric factors (see Introduction) and assumes that the cavity size curves are based on an accurate model and a well tuned force field if they are based on molecular mechanics (see comment above).

energy (see Fig. 1b) the ligand may be preorganized for a metal ion M^a with a structure of the $M^a(L)$ complex close to the lower energy minimum (short bonds) and less preorganized (higher energy ligand conformation) for a metal ion M^b with a structure of the $M^b(L)$ complex close to the higher energy minimum (long bonds). Examples, where different ligand conformations with similar energy are observed for different metal ions include the macrocycle cyclam (1,4,8,11-tetraazacyclotetradecane, see L^2 in Chart 2 below; *cis*- and *trans*-$[M(cyclam)X_2]^{n+}$ geometries), [13] the δδ- and λδ-conformers of metal complexes with *trans*-diammac (diammac = 6,13-diamine-1,4,8,11-teraazacyclotetradecane) [27] or those with sar-type hexaamine cage complexes [28]. If the structures of $M^a(L)$ and $M^b(L)$ both are close to the corresponding minima in Fig. 1b, the ligand is complementary for both metal ions, M^a and M^b. It emerges again that preorganization and complementarity are two different but equally important features.

Different conformers of a ligand are formed by rotation about one or more single bonds in the ligand backbone. These are relatively low energy processes and, often, there is a set of conformers with only small energy differences. Therefore, conformational flexibility always leads to a loss of selectivity. This is obvious from Fig. 1c, which visualizes a typical situation of a ligand with a cluster of conformations with similar energy and different cavity size. Note that here it is appropriate and important for our arguments to make a difference between flexibility (conformational freedom, a set of curves in Fig. 1) and elasticity (deformation of a specific conformer, single curve in Fig. 1). There is another type of ligand flexibility, i.e. that due to multiple configurations (e.g. with coordinated amine donors). Clearly, this is only a possible differentiation for the coordinated ligand. A specific conformation of the metal-free ligand may have an ideal shape (a high degree of preorganization) for each configuration in the complex[4]. The effects of conformational and configurational flexibility are similar, i.e. a reduction of selectivity.

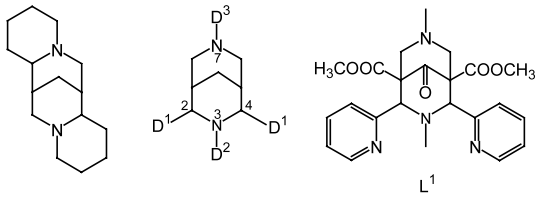
The quite general conclusion is that rigid ligands may be more selective. They may lead to a peak selectivity, i.e. strongly discriminate between metal ions due to size match selectivity. The more flexible ligands often lead to a plateau selectivity, i.e. the conformational flexibility allows the ligand to adjust for various metal ion sizes [29]. This is, e.g. the case with most simple tetraaza macrocyclic ligands, and these, quite generally, belong to the class of hosts best visualized by a set of potential energy curves, such as those in Fig. 1c [9,13,30–32].

There is another fundamental idea which needs to be discussed here, the distinction between elasticity of a ligand and that of a coordination sphere. A good example to discuss this is 1,10-phenanthroline. This is a very rigid molecules (both with respect to flexibility and elasticity), and the out-of-plane distortion of the ligand backbone and of the entire metal–ligand fragment are very energetically unfavorable processes. However, with changing size and electronic preferences of the metal ion the coordination center has some freedom to move within the ligand plane (short or long metal-donor bonds). This may lead to some distortion of the metal–nitrogen–carbon angle but the corresponding potentials are often relatively weak. Macrocyclic ligands with aromatic groups, such as porphyrins, prevent such a distortion (elasticity of the coordination sphere), and relatively small conformational changes in the ligand and/or a movement of the metal center out of the ligand plane are then the only possible modes of distortion.

6. Two case studies

6.1. Tetradentate bispidine-type ligands

The bispidine backbone is derived from the natural product sparteine (see Chart 1), and tetradentate bispidine derivatives of the type of L^1 have been described some time ago [33] (due to the two-fold Mannich condensations the bispidine-type ligands discussed here are bispidinones (3,7-diazabicyclo[3.3.1]nonanone, the 9-keto group is, upon coordination, often hydrated); the substituents at C^1 and C^5 (usually methylester groups) and the 9-keto group are omitted in most Figures in this article). However, their rich coordination chemistry has only started to be developed in recent years [34–41]. Four-, five- and six-coordinate ligands with various donor sets (pendent donors at positions 2,4-, 2,3,4-, 2,4,7- or 2,3,4,7-), and ligands with one or two bispidine cavities (linked at amines N^7), as well as their transition metal complexes have been reported. Here, we will concentrate on the tetradentate ligand L^1 with two tertiary amine and two pyridine donors (Chart 1).



L^1

Chart 1.

[4] Note that conformational flexibility is also different for coordinated and metal-free ligands since ligand coordination may restrict its conformational freedom. In general, this is of no influence with respect to the cavity size curves since these are computed with a dummy metal ion (this is a deficiency of the cavity size curves which needs to be remembered).

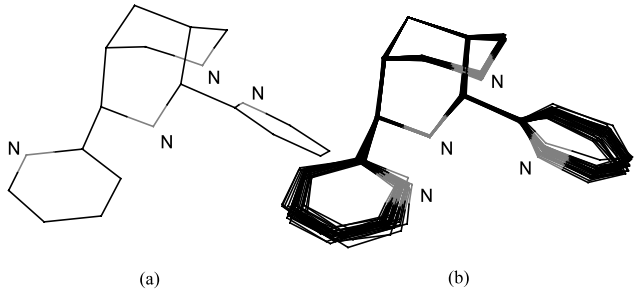


Fig. 2. (a) Plot of the ligand backbone of the experimentally determined structure of the bispidone L^1; [35] (b) overlay plot of the ligand backbones of L^1 from 40 experimental structures of $M(L^1)(X)_n$ complexes ($n = 1,2$; co-ligands and substitutes to L^1 omitted) [38].

The preferred geometry of L^1 is the chair–chair conformation with the 2,4-pyridine substituents in equatorial orientation [34,42,43], i.e. the same geometry as observed in the complexes. The only notable flexibility is a free rotation of the pyridine groups around the $C^{2/4}$–$C^{\alpha}_{pyridine}$ single bonds, and in crystal structures the metal-free ligand L^1 and its derivatives have the pyridine nitrogen donors rotated away from the center of the bispidine cavity by ca. 180° [36,37,39]. Thus, the 3,7-diazabicyclco[3.3.1]nonanone-part of the bispidine ligand L^1 is highly preorganized; the rotation of the pyridine substituents around the $C^{2/4}$–$C^{\alpha}_{pyridine}$ bonds are low energy processes; there is only one coordinating conformation of L^1, and this is complementary for geometries derived from *cis*-octahedral coordination (including square pyramidal (five-coordinate) and pentagonal bipyramidal (seven-coordinate, with one extra in-plane ligand)). A plot of the experimental molecular structure of the metal-free ligand is given in Fig. 2a, and Fig. 2b is an overlay plot of the ligand part of 40 structures of $[M(L^1)X_n]^{m+}$ complexes {$n = 1,2$; M = Cr(III), hs Mn(II), hs Fe(II), hs Co(II), Cu(II), Cu(I), Zn(II)} [34–41]. It emerges that the ligand is very rigid (inflexible apart from the rotation of the pyridine groups) and inelastic. Together with the complementarity for *cis*-octahedral and corresponding geometries, steep single minimum hole size curves (such as that in Fig. 1a) and a high degree of selectivity towards the metal ions for which it has an optimum fit, might be expected[5].

Shown in Fig. 3, curve (a) is the computed cavity size curve for ligand L^1. In contrast to the naïve expectation above this is very flat. Inspection of the computed structures along the curve indicates that the ligand geometry is, as expected (see Fig. 2b) constant, i.e. very rigid (except for the weak torsional mode involving the pyridine groups, see above). However, the metal ion is practically free to move out of the center of the cavity, i.e. while the ligand is inelastic, the coordination sphere has a high degree of elasticity. That is, in terms of steric effects, the ligand L^1 induces a very low degree of differentiation in terms of complementarity with virtually all first row (and probably also second row) transition metal ions (1.95 Å < M–$N_{average}$ < 2.3 Å, derived from Fig. 3, curve a). Note that the degree of complementarity difference is expected to increase when electronic effects (preference for specific donors) are included (generalized double complementarity, see Introduction). With metal-donor bonding potentials included (see Fig. 3, curve b for cobalt(II)) the potential energy surface is steep; note that this curve is for the hypothetical case $[Co^{II}(L^1)]^{2+}$, i.e. without co-ligands, L^1 without substituents at C^1, C^5, C^9. From the structural data of all known complexes [40] it follows that the metal-donor distances vary over a wide range (sum of the four M–N distances: 8.21–9.41 Å, i.e. a variation of ca. 0.28 Å per M–N bond). This is in agreement with the interpretation of the hole size curves:

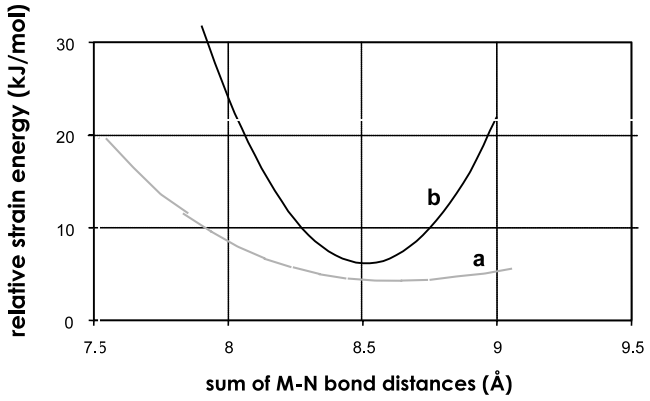


Fig. 3. Hole size curves, i.e. strain energy induced to the ligand backbone of L^1 by increasing or decreasing the metal ion size from its best fit size; note that the technique used constrains the sum of all (dummy) metal-donor distances, i.e. each individual bond distance and thus the shape of the coordination polyhedron is unconstrained [26]; (a) metal-free ligand (no strain of metal-donor bonds included), (b) one isomer of the cobalt(II) complex fragment $Co(L^1)^{2+}$, see Fig. 4.

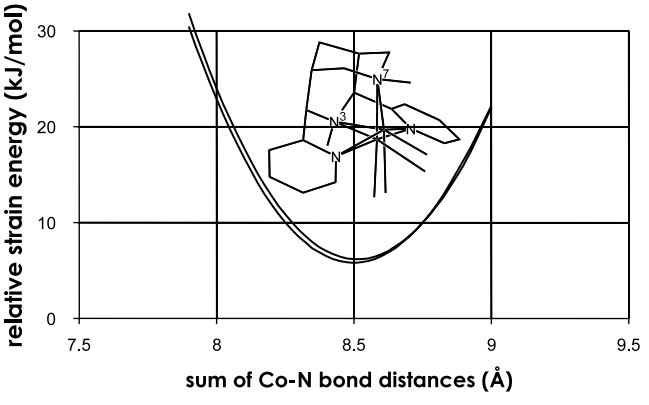


Fig. 4. Hole size curves (see also caption of Fig. 3) of the two isomers of $Co(L^1)^{2+}$ (see inserted structural plot) [38].

[5] Note again that this argument is only based on steric effects which might not be the only or major contribution to metal ion selectivity (see above and [8]).

while the ligand is very rigid, there is a high degree of elasticity in the coordination sphere.

Another interesting feature with respect to the elasticity of the coordination sphere of complexes of L^1 is that there are two isomers, with $M–N^3 \geq M–N^7$ or $M–N^3 < M–N^7$ (see structural plots in Fig. 4). Also shown in Fig. 4 are the two strain energy versus sum of cobalt(II)–N distance curves, one for each distortional isomer. The similarity of the curves means that the energies are similar, which means both forms might be observed (note, however, that the molecular mechanics analysis does not include electronic (and structural) effects of the co-ligands). Indeed, it was possible to obtain structural data of the two forms: with NO_3^- and OAc^- (bidentate each) $Co–N^3 = 2.14$, 2.15 Å, $Co–N^7 = 2.13$, 2.17 Å with $(OH_2)_2$ (two structures with different anions) $Co–N^3 = 2.16$, 2.15 Å, $Co–N^7 = 2.22$, 2.21 Å [40].

With copper(II) all structures of L^1 are five-coordinate and square pyramidal; these are unusual for $Cu^{II}N_4X$ chromophores because all $[Cu(L^1)X]^{n+}$ complexes have the co-ligand in-plane and an axial amine ($Cu–N^3_{av} = 2.03$ Å, $Cu–N^7_{av} = 2.30$ Å; shown in Fig. 5 is a plot of the molecular structure of $[Cu(L^1)(Cl)]^+$) [36]. DFT calculation indicate that, while L^1 enforces this highly unusual coordination geometry, it is not much strained (energization of only ca. 10 kJ mol^{-1} with respect to the usual CuN_4X geometry with axial co-ligands) [44]. That is, L^1 has a high complementarity for copper(II) in general, and specifically for copper(II) in this unusual coordination geometry. This leads to very interesting properties for $[Cu(L^1)X]^{n+}$, such as unusually stable dicopper(II)-peroxo compounds, short and strong Cu^{II}–Cl bonds and high and tunable activities in aziridination catalysis [36,37,41,45].

In conclusion, due to the rigid adamantanoide backbone the bispidine-type ligand L^1 is complementary for *cis*-octahedral-type geometries. However, there is considerable elasticity in the coordination sphere; (i) there are two slightly but significantly different coordination sites in the cavity, which can accommodate metal ions with different electronic preferences, and (ii) the rigid ligand tolerates large differences in M–N bond distances. Hole size curves are, therefore, not useful for analyzing differences in terms of stabilities and molecular properties with various metal ions because the ligand does not differentiate in terms of metal ion size (no size match selectivity). With copper(II) L^1 leads to stable complexes, although the enforced square pyramidal coordination sphere with an axial amine and an in-plane co-ligand ($NCCH_3$, Cl^-, OH_2) is unusual, and this leads to exciting reactivities. The energization of this state is minimal. Therefore, bispidine derivatives of the type of L^1 are excellent examples to demonstrate that rigidity and elasticity (of the coordination sphere), as well as the lack of entasis and high reactivities are not mutually exclusive.

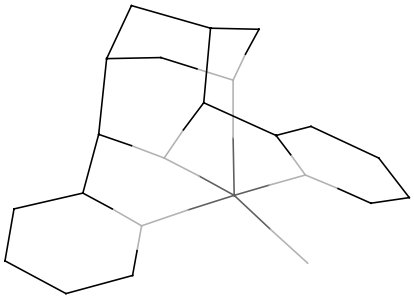


Fig. 5. Plot of the experimentally determined structure of $[Cu(L^1)(Cl)]^+$ [34].

6.2. Reinforced macrocyclic ligands

The 16-membered macrocyclic tetraamine ligand cyclam (L^2, see Chart 2) is the prototype of a tetraazamacrocycle. Due to the appropriate hole size in a specific configuration and conformation, see below, L^2 forms very stable transition metal complexes with relatively high in-plane ligand fields (four secondary amine donors in a planar arrangement) with various transition metal ions, especially with nickel(II) and copper(II) [46–48]. This, together with structural data [49] indicates that L^2 is highly complementary towards copper(II) and nickel(II).

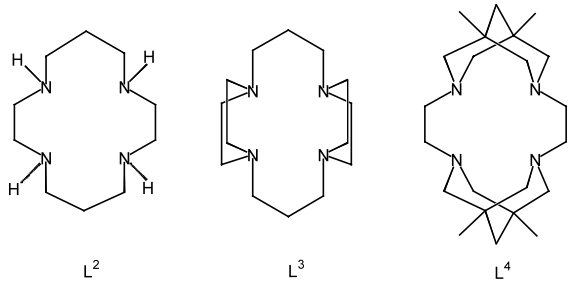


Chart 2.

The fully saturated ligand backbone suggests that the metal-free ligand is highly flexible [9,13,30–32]. In the coordinated ligand the configurational flexibility due to the four chiral amine donors (five possible *trans*-configurations with different relative orientations of the amine protons; the corresponding *cis*-configurations are not explicitly considered here) [50] and the conformational flexibility of the five- and six-membered chelate rings (δ or λ; chair, skew-boat or boat, respectively) lead to an envelope over a number of possible hole size curves with widely varied optimum metal ion size, such as the situation shown in Fig. 1c [9,10,13]. A number of conformational analyses of L^2 derivatives and their metal complexes confirm this expectation [51,52]. An important feature is that the dipole–dipole repulsion due to the amine donor lone pairs leads to a destabilization of highly preorganized metal-free ligand structures, such as those with the lone pairs directed

towards the center of the cavity (see notes on the cavity size curves and on conformations stabilized upon coordination of the ligand elsewhere in this paper). It emerges that hole size curves are not appropriate for analyzing the ligand preorganization of L^2. Another molecular-mechanics-based approach to compute and analyze ligand preorganization and complementarity for this type of ligands has been described, [53] and conformational analysis clearly is the tool of choice for the analysis of preorganization.

For an efficient ligand preorganization for a specific geometry the configurational and conformational flexibilities need to be reduced. The cyclam derivatives L^3 and L^4 (see Chart 2) are two published examples where this has been achieved [54–59]. Both, L^3 and L^4 have four tertiary amine donors. For these ligands there is no configurational flexibility (the coordinated donors are achiral), the conformational flexibility of the five- (L^3) or six-membered (L^4) chelate rings is much reduced and, together with the increased nucleophilicity of the tertiary amines this should lead to a high electronic complementarity. Therefore, increased stabilities and in-plane ligand field strengths might be expected[6].

There are no crystal structures of copper(II) complexes of L^3 and L^4, and the series of stability constants is not available. However, on a qualitative basis the stability of $[Cu(L^n)(OH_2)_x]^{2+}$ ($n = 2, 3, 4$; $x = 0, 1, 2$) seems to increase along the series $L^2 \sim L^3 << L^4$ [56,57]. An intriguing feature is that the ligand field induced by L^3 ($\lambda_{max} = 540$ nm) is lower than that induced by L^2 ($\lambda_{max} = 500$ nm), while $[Cu(L^4)]^{2+}$ has the highest energy dd transition observed so far for copper(II) tetraamines ($\lambda_{max} = 390$ nm, that of $[Cu(L^4)(OH_2)_x]^{2+}$, $x = 1$ or 2, is 430 nm, see Table 1)[6].

Fig. 6 shows computed structures of the coordinated ligands L^2, L^3 and L^4 (copper(II) complexes; two axial OH_2 donors for L^2; L^3 and L^4 have been computed as four-coordinate complexes; the metal ion was deleted in all structures shown, and the lone pair directions of the amine donors have been computed and added to visualize the ligand complementarity[7]. Shown in Fig. 6 are one conformation each for $[Cu(L^2)(OH_2)_2]^{2+}$ (*trans*-III, λδ) and $[Cu(L^3)]^{2+}$ (chair–chair), and two conformations for $[Cu(L^4)]^{2+}$ (λδ and δδ). The structure shown for L^2 is that observed in copper(II) and nickel(II) complexes and that which is computed as the lowest energy geometry [9,10,13,18,49,61–64]. The two structures of L^4 are nearly degenerate [57]. The structure shown for L^3 has an enforced square planar geometry, the lowest energy computed structures of the metal-free ligand and of the copper(II) complex are different from that shown here. That of the ligand is twisted to prevent the unfavorable boat conformations of the two 1,4-diazacyclohexane fragments; that of the copper(II) complex is square pyramidal with the copper center above the N_4 plane. That is, the stresses built in the backbone to preorganize the ligand lead to considerable distortion and strain, i.e. the design of the ligand is less than satisfactory. The second problem is that the lone pairs are misdirected, bonding to a metal ion in a planar geometry does not lead to optimal stabilization, i.e. there is a lack of electronic complementarity and a distortion towards square pyramidal geometry, which relieves some steric strain and leads to a significant loss of electronic interaction energy. Thus, L^3 does not fulfill the hope of increased stability and ligand field. This is different for L^4: The reinforced six-membered chelate rings are virtually strain-free, both conformations (λδ and δδ) are of similar stability (crystallographically analyzed is the λδ-form of the ligand) and both (especially the δδ form) have the lone pairs directed towards the metal center. Thus, L^4 is highly preorganized for planar or 4+2 (4+1) coordination, e.g. for copper(II), and it is highly complementary for copper(II).

The optimum structures of the three copper(II) complexes with L^2, L^3 and L^4 (various conformations, four-, five- and six-coordinate complexes) were refined with molecular mechanics, and the optimized structures were validated and found to be of good quality, based on the experimental structure (cyclam complex) or by comparison of the experimental electronic spectra with those obtained from angular overlap model (AOM) calculations, based on the computed structures (MM-AOM method, see Table 1) [65].

One conclusion of this paragraph is that, in contrast to a widely and uncritically accepted opinion and misinterpretation, tetraazamacrocyclic ligands, cyclam (L^2) in particular, are not highly preorganized towards any particular coordination geometry. A major reason for the large stability with copper(II), e.g. is a high degree of complementarity for copper(II) in particular (other factors not discussed in detail in this paper include electronic effects, entropy and solvation). Another important factor is that cavity size curves for macrocyclic ligands such as L^2 do not produce any useful and realistic information on the degree of ligand preorganization, even if the entire set of curves are used (Fig. 1c) and if metal ion independence is given by the approach used. This is because all current (molecular-mechanics-based) methods use a dummy metal center, and this enforces a lone pair direction of the donor atoms towards the metal center. For the visualization and quantification of the ligand complementarity this does not lead to a problem, and hole size curves for

[6] Complex stabilities and ligand field strengths are often correlated. However, there is no fundamental reason why this should generally be the case.

[7] A similar approach to visualize lone pair directionality has been used before [60].

Table 1
Experimentally determined and computed (MM-AOM) electronic transitions of $[Cu(L^2)(OH_2)_2]^{2+}$, $[Cu(L^3)(OH_2)_n]^{2+}$ and $[Cu(L^4)(OH_2)_n]^{2+}$ ($n = 0$, 1, 2) [57]

Compound	$E_1(xz)$ [a,b]	$E_2(yz)$ [a,b]	$E_3(xy)$ [a,b]	$E_4(z^2)$ [a,b]
$[Cu(L^2)(OH_2)_2]^{2+}$ ($n = 1$, 2) (exp.) [66]	19 900 (500)			
$[Cu(L^2)(OH_2)_2]^{2+}$ (calc.)	19 200	20 020	20 400	13 600
$[Cu(L^3)(OH_2)_n]^{2+}$ ($n = 1$, 2) (exp.) [56]	18 590 (540)			
$[Cu(L^3)(OH_2)]^{2+}$	18 654	20 330	17 506	16 590
$[Cu(L^3)(OH_2)_2]^{2+}$	21 070	21 600	20 395	17 225
$[Cu(L^4)(OH_2)^n]^{2+}$ in H_2O (exp.) ($n = 1$, 2)	23 250 (430)			~19 200 (520)
λλ-$[Cu(L^4)(OH_2)_2]^{2+}$ (calc.)	23 000	23 380	22 120	19 530
λδ-$[Cu(L^4)(OH_2)_2]^{2+}$ (calc.)	23 560	23 640	22 650	19 640
$[Cu(L^4)]^{2+}$ in $MeNO_2$ (exp.)	25 640 (390) [c]			
λλ-$[Cu(L^4)]^{2+}$ (calc.)	24 660	25 040	23 400	23 580
λδ-$[Cu(L^4)]^{2+}$ (calc.)	24 660	25 220	23 770	23 770

[a] In cm^{-1} (nm); arbitrary assignment.
[b] See [65] for AOM parameters.
[c] Single unresolved band.

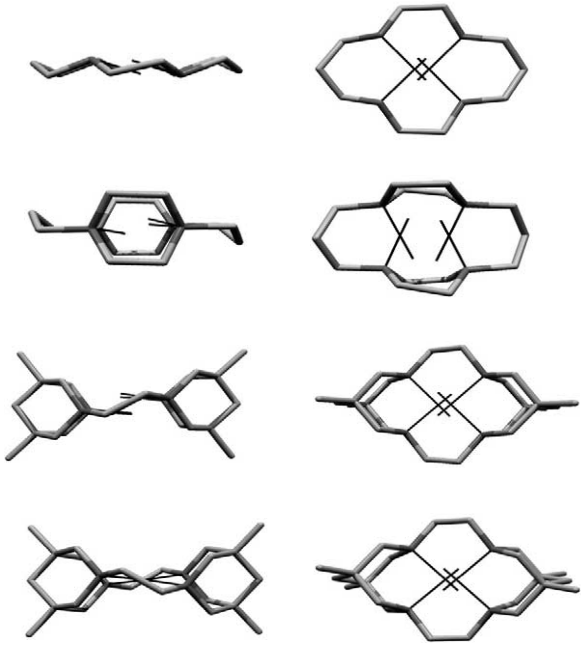


Fig. 6. Plots of computed structures of the copper(II) complexes of L^2, L^3 and L^4 (metal ion omitted, computed direction of the lone pairs included; see text).

macrocyclic ligands are, therefore, a valuable tool for the computation of ligand complementarity. For ligand preorganization conformational analysis is the method of choice.

Note, that with respect to the scope of hole size curves the two examples discussed in this review (complexes of L^1 and those of L^2, L^3, L^4) lead to completely different conclusions. Remember also that preorganization refers to conformational flexibility and complementarity to elasticity, both with respect to a specific metal ion and coordination geometry. For selective stabilization (e.g. metal ion selectivity), as well as for destabilization (entasis) the combination of both effects are of importance. The general conclusion, therefore, is that, while a thorough understanding of fit and misfit between hosts and guests is of importance in many areas, even with clear concepts, their computation and visualization may not be straight forward.

Finally, it is worth considering the results of the highly preorganized (for square planar geometry), complementary (e.g. for copper(II)) and very rigid macrocycle L^4 again (Chart 2, Fig. 6, Table 1). A careful design has helped to create an exciting new ligand with predictable and extraordinary properties. The synthesis was, as expected, demanding; however, it is now possible to prepare the ligand in gram quantities [57–59]. The remaining and considerable problem is that complexation of this ligand has only been achieved in very low yield, and this still remains to a large extent an unsolved preparative problem; once formed the complex is very stable but the inflexibility of the ligand and the extremely high basicity of the amine donors are reasons why the general synthetic procedures fail to produce the desired complexes in significant yield [57]. That is, the additional limits for the experimentalist are that high degrees of preorganization and complementarity, an excellent fit, do not necessarily lead to the straight forward synthesis of stable compounds.

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